

# **Cognitive decline in preclinical Alzheimer's disease**

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**Harvard Aging Brain Study**

**MCI Symposium 2017**

# Longitudinal cognitive decline in A $\beta$ + normals

## *Episodic Memory*

**Lim 2013** (LM+CVLT; Rey+1 card learning+1 Back)

**Snitz 2013** (Rey)

**Clark 2016** (RAVLT DR, LMDR, BVMT DR)

## *EF & Semantic Memory*

**Snitz 2013** (TMT B, TMT A, CAT)

**Wirth 2013** (Stroop+Controlled Oral Word Association test+TMT A+Digit Sym)

**Clark 2016** (TMT B, Stroop, Digit Symbol)

**Papp 2016** (CAT)

## *Global & Functional*

**Storandt 2009** (all cognitive composites)

**Resnick 2010** (MMSE)

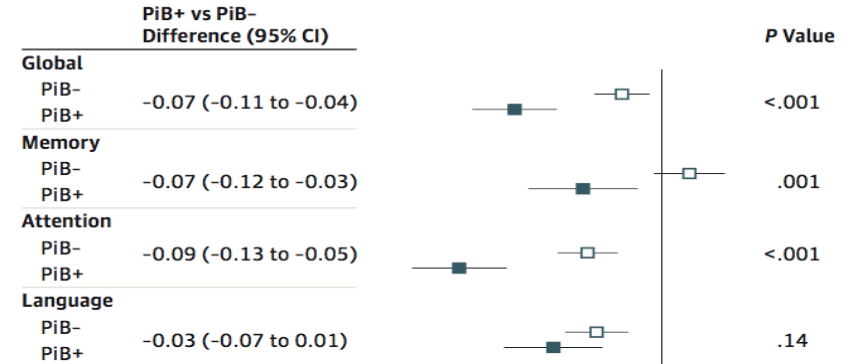
**Villemagne 2011** (MCI)

**Doraiswamy 2012; Landau 2012** (ADAS-cog)

**Roe 2013** (CDR)

**Rowe 2013** (MCI/dementia)

## MCSA



*Petersen 2016 JAMA Neurol*  
*n=564, follow-up=2.7*

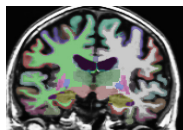
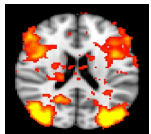
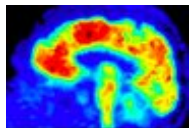
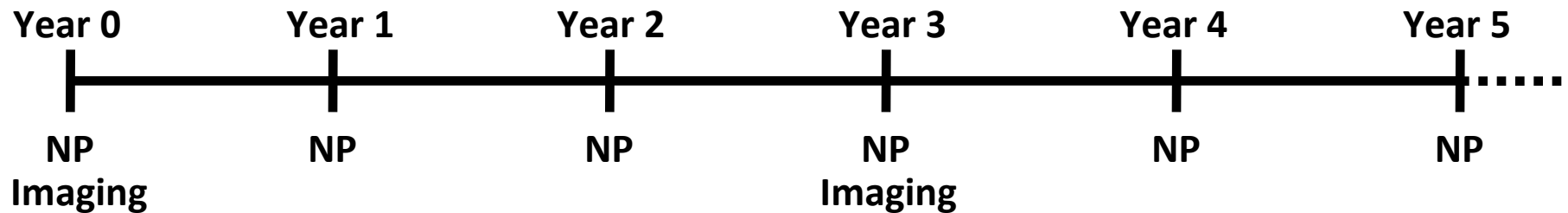
# Harvard Aging Brain Study (HABS)

## Baseline Criteria

CDR=0

Age 60-90

MMSE>25



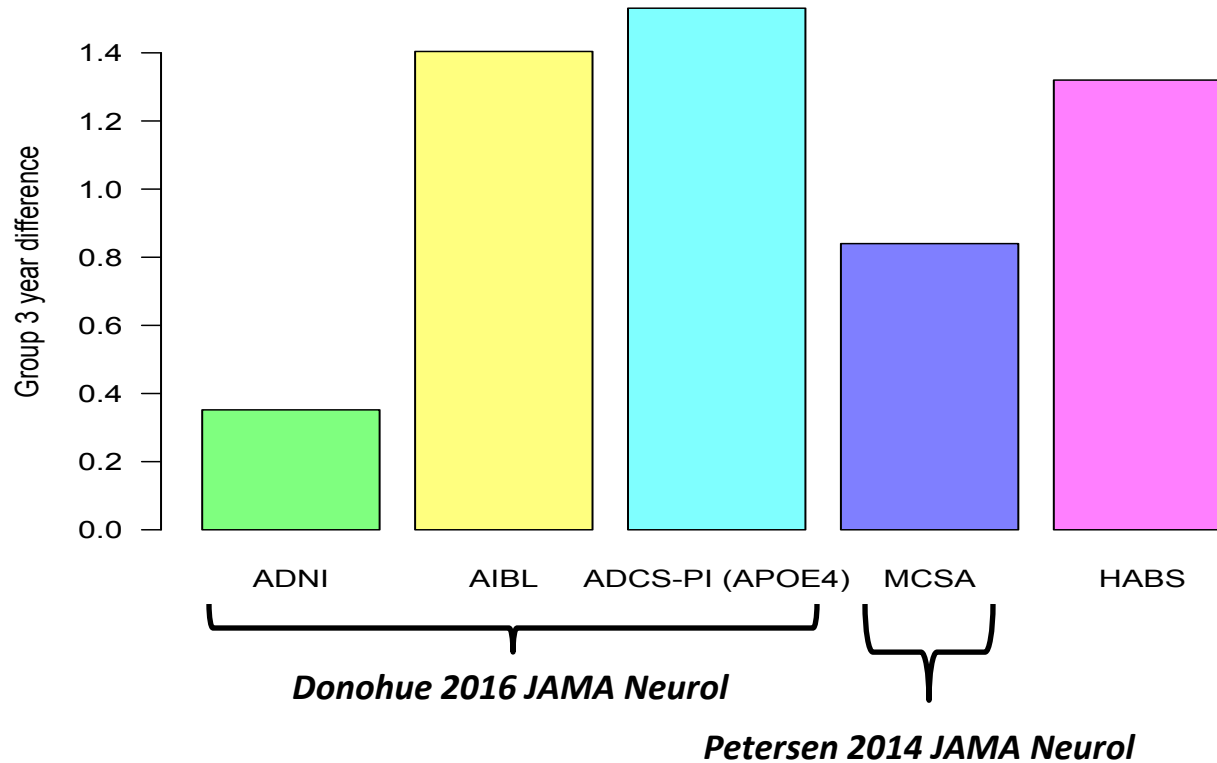
	All HABS	A $\beta$ -	A $\beta$ +
N	277	206 (74.4%)	71 (25.6%)
Age	73.5 $\pm$ 6.0	72.9 $\pm$ 6.0	75.2 $\pm$ 5.7
Female	59.2%	58.7%	60.6%
Education	15.8 (3.1)	15.6 (3.1)	16.4 (2.8)
APOE4+	29.3%	18.4%	61.2%
Follow up (years)	3.6 $\pm$ 1.3	3.5 $\pm$ 1.3	3.7 $\pm$ 1.2

N=134 with T807 Imaging (~Year 3)

**HABS: A $\beta$ + show decline on the Preclinical Alzheimer's  
Cognitive Composite (PACC)**

## A $\beta$ effect across cohorts

*HABS A $\beta$  difference = -0.11 z-score units/year*



**HABS: A $\beta$ + show decline across cognitive composites**

## **Independent decline in episodic memory and semantic memory**

## Decliner Subtypes within A $\beta$ +?



**Decline across domains tracks with anatomy**

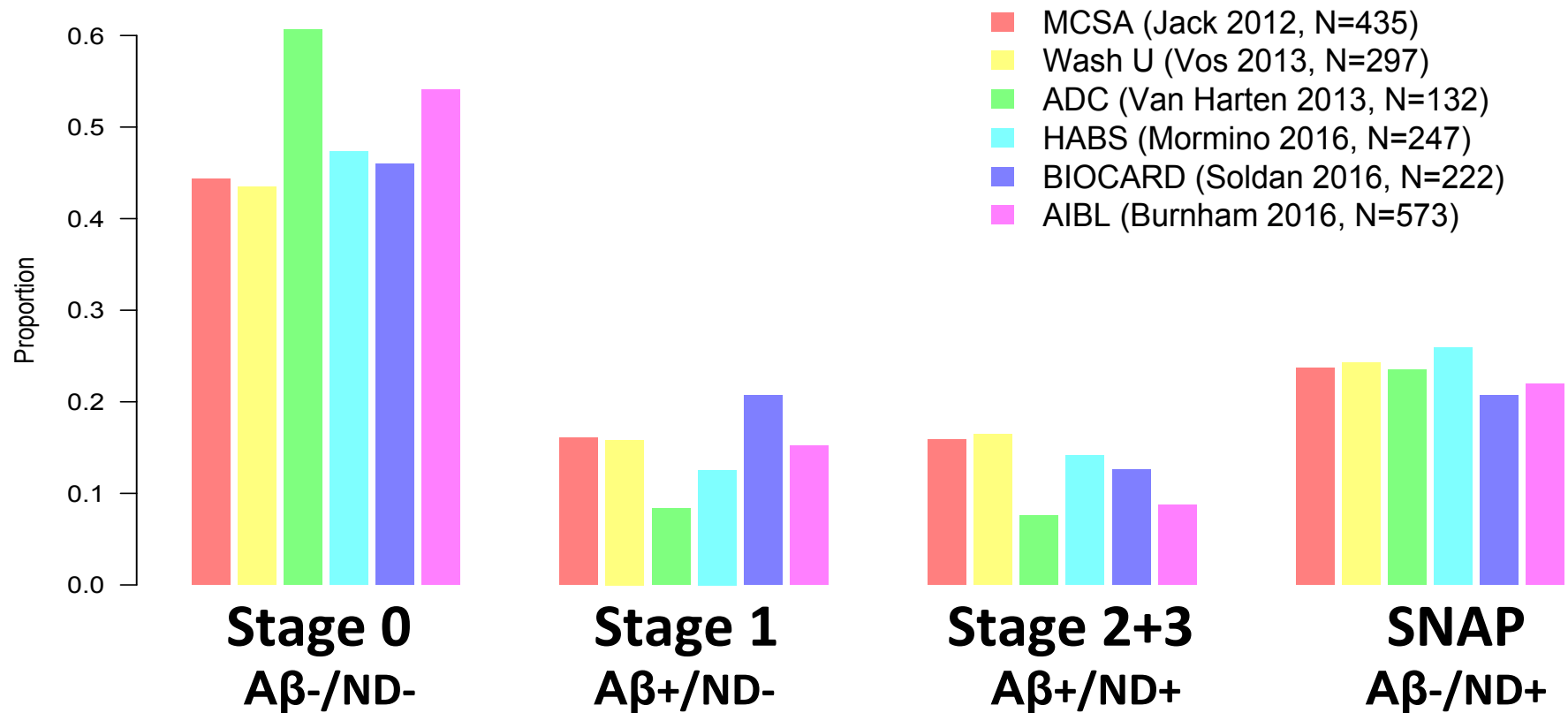
**A $\beta$  difference earlier for Free versus Cued Recall**

## **A $\beta$ difference in Free Recall among CDR stable subgroup**

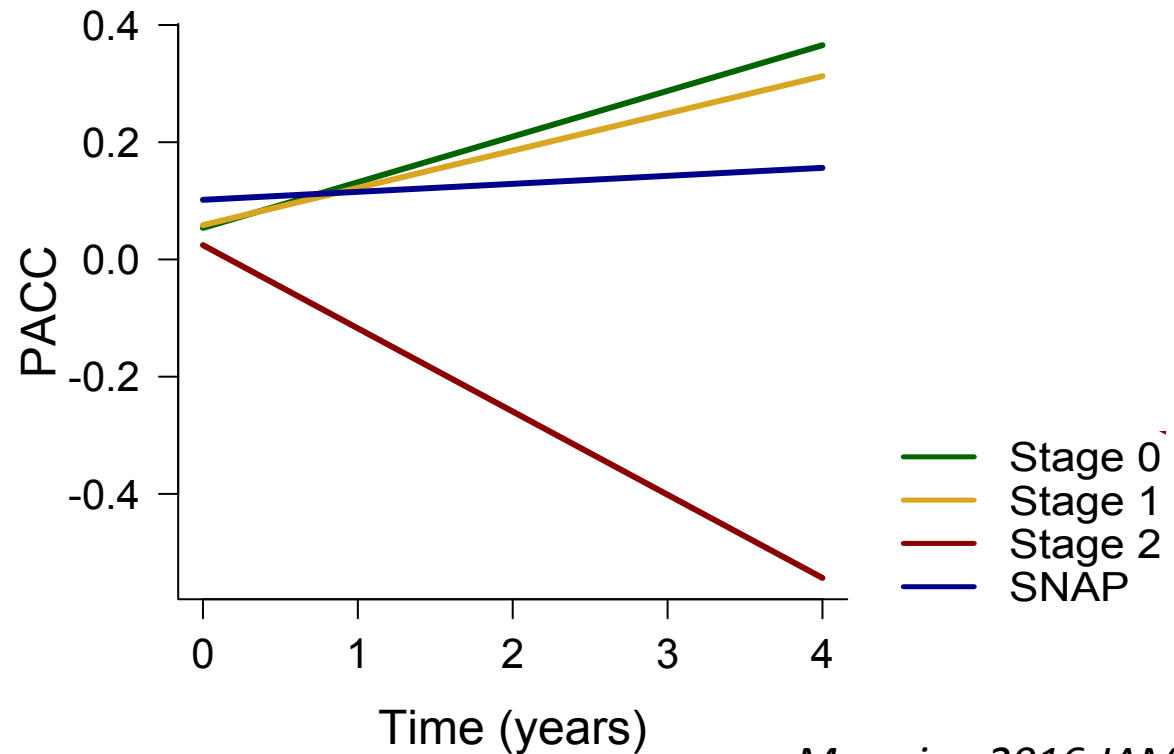
# NIA-AA 2011 Preclinical Staging Criteria

		MRI (hippocampus, AD-like) FDG (AD-like) CSF (Tau, pTau)	
		ND-	ND+
Amyloid PET CSF A $\beta$	A $\beta$ -	Stage 0	SNAP
	A $\beta$ +	Stage 1	Stage 2

# NIA-AA preclinical stages across normal cohorts



## PACC decline greatest in NIA-AA Stage 2

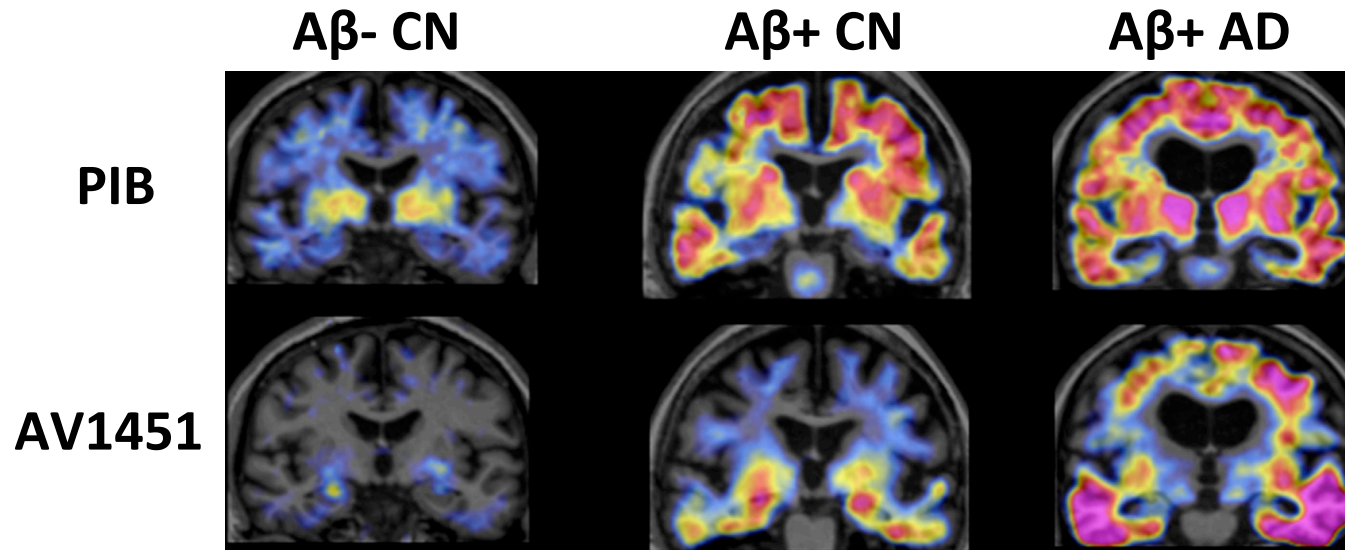


*Mormino 2016 JAMA Neurol*

**Others=Vos 2013 Lancet Neurol, Soldan 2016 JAMA Neurol, Burnham 2016 Lancet Neurol**

## **NIA-AA Stage 2 shows multi-domain decline**

# Tau PET Imaging in HABS



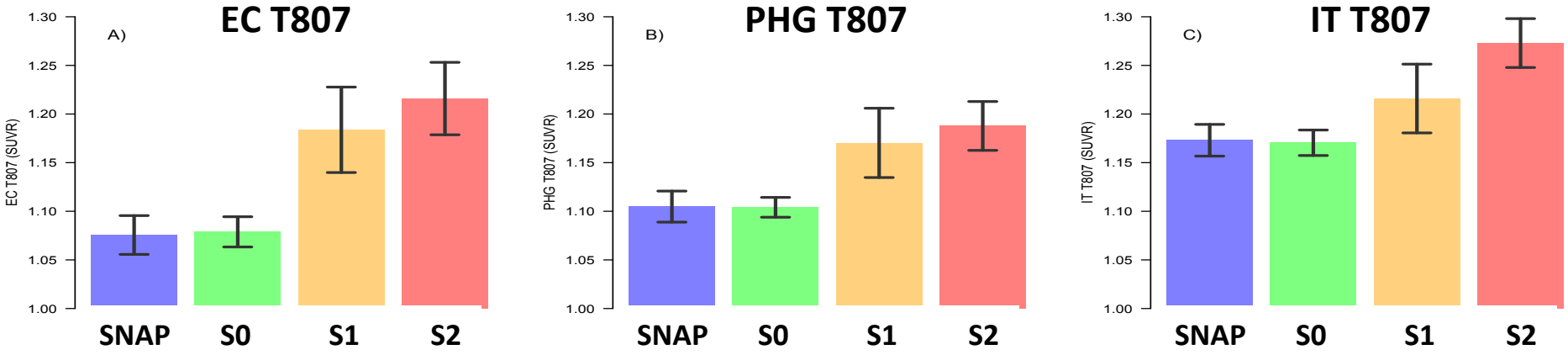
*Sperling, Mormino, & Johnson, 2015 Neuron*

**HABS T807  
Sample**

	All	Aβ-	Aβ+
N	134	92	42
Age	76.2 (6.2)	75.3 (6.4)	78.3 (5.4)
Female	75	51	24
Ed	15.9 (3.0)	15.7 (3.1)	16.2 (2.7)



# Tau PET more specific for A $\beta$ than ND markers



*Mormino 2016 JAMA Neurol*

**Elevated Tau predicts decline among A $\beta$ +**

## Summary

- **A $\beta$ + normals demonstrate longitudinal cognitive decline**
- **Decline is present across multiple domains**
  - **Subtypes within preclinical AD?**
- **Neuropsychological tests vary in ability to detect change that occurs early versus change more proximal to functional decline**
- **Positive ND markers and Tau predict decline within A $\beta$ +**
  - **Tau PET specific for A $\beta$**
  - **ND markers influenced by multiple etiologies (ie. TDP-43?)**

# Harvard Aging Brain Study

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